Complete Summary

GUIDELINE TITLE

Imatinib mesylate (Gleevec™) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, Sarcoma Disease Site Group. Imatinib mesylate (Gleevec) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 6. 23 p. (Evidence-based series; no. 11-7). [46 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing KIT (CD117+)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether treatment with imatinib mesylate (Gleevec™) has palliative benefit, in terms of tumour response, disease progression, survival, or quality of life, for patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing the KIT tyrosine kinase receptor (identified by CD117 immunohistochemical staining)

TARGET POPULATION

Adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) expressing KIT (CD117+)

INTERVENTIONS AND PRACTICES CONSIDERED

Imatinib mesylate (Gleevec™) therapy

MAJOR OUTCOMES CONSIDERED

- Tumour response
- Disease progression
- Survival
- Toxicity
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches of MEDLINE (1996 through December 2005), EMBASE (1996 through December 2005), PREMEDLINE (to June 25, 2003), and the Cochrane Library (2005, Issue 4) were undertaken. Search terms used included "gleevec," "glivec," "imatinib," or "STI571" in combination with "GIST" or "gastrointestinal stromal".

In addition, the conference proceedings of the American Society of Clinical Oncology (ASCO) were searched for abstracts of relevant trials, for the years 1996-2005. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov) was also searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were eligible for inclusion in the systematic review conducted for this practice guideline if they were:

- Abstracts or full reports of randomized phase II and III clinical trials of imatinib mesylate as treatment for adult patients (≥15 years of age) with unresectable or metastatic gastrointestinal stromal tumours (GIST) that reported data on one or more of the following outcomes: objective response rate, stable disease rate, progression-free survival, overall survival, toxicity, and quality of life
- Systematic reviews (meta-analyses or practice guidelines)

Exclusion Criteria

Articles were excluded if they were retrospective studies, editorials or letters, or articles that were published in languages other than English. A post hoc decision was made to remove all phase I studies that were originally included in the results section of this document as there were available data from phase II and phase III trials.

NUMBER OF SOURCE DOCUMENTS

Three phase III and two phase II studies were reviewed

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data were not pooled as only abstract/interim data were available for two of three studies.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Sarcoma Disease Site Group (DSG) of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on imatinib mesylate (Gleevec™) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The Sarcoma DSG focused their discussion on the evidence for imatinib as a treatment for adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST). Three of the trials (two phase III and one phase II) were only available in abstract form. Therefore, full data was not available for all outcomes, thus making pooling of the results inappropriate. The remaining phase II trial was available as a fully published report. The trial received funding from Novartis Oncology. Since those trials constituted the best available evidence for the use of imatinib for gastrointestinal stromal tumours, the Sarcoma DSG agreed that those trials should be included in this practice guideline report.

The Sarcoma DSG also discussed the fact that no trials compared imatinib to no treatment. Therefore, it is not possible to state with absolute statistical certainty that treatment with imatinib confers a definite survival advantage. However, the trials do show response rates ranging from 41% to 58%. If the stable disease rate is added to the response rate, the result is an increase to 73% to 82%. Also, progression-free and overall survival in those trials is markedly higher than in historically untreated patients. Therefore, the Sarcoma DSG agreed that it is reasonable to assume that the observed progression-free and overall survival rates are both relevant and meaningful.

Another point of discussion was the question of dose level. There has been no established benefit for doses higher than 400 mg daily. In addition, the higher toxicity associated with higher doses of imatinib would suggest that there is no clear benefit to starting patients at higher doses. Therefore, the Sarcoma DSG recommends that patients should start on a dose of 400 mg daily.

Finally, in terms of treatment duration, there are limited data to form definitive recommendations for situations such as stable disease, disease that is rendered resectable, or complete remission of disease. However, given the data that are available in the trials conducted to date, as well as the potential toxicity and the

difficulty in discerning complete remission with reasonable certainty, the Sarcoma DSG agreed on the following:

1. For stable disease, treatment should be discontinued if the disease progresses or toxicity develops.
2. For disease that is rendered resectable, surgery should be considered.
3. For complete clinical response (CR) and radiologic remission, the discontinuation of therapy two months after CR has been observed would be reasonable.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following review and discussion of sections 1 and 2 of this evidence-based series the Sarcoma Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 179 practitioners in Ontario (two pathologists, 26 radiation oncologists, 45 medical oncologists, and 106 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on March 24, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The DSG reviewed the results of the survey.

This practice guideline report reflects the integration of the draft recommendations with feedback obtained from the external review process. The report has been approved by the Sarcoma DSG and circulated to the members of the Report Approval Panel (RAP) for review and approval.

Report Approval Panel

The report was reviewed and approved in March 2006 by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- In patients with KIT-expressing (CD117+) unresectable or metastatic gastrointestinal stromal tumours (GIST), treatment with imatinib is a recommended therapy.
- Until additional data become available, the initial dose of imatinib should be prescribed at a dose of 400 mg daily. A dose of 400 mg twice daily may be considered in patients who demonstrate progression on the lower dose.
- The optimal duration of therapy in responding patients or in those patients who achieve a complete clinical and/or radiologic remission has not yet been defined. Phase III trials have demonstrated benefit for up to two years of continued therapy.
- Eligible patients with gastrointestinal stromal tumours who do not respond adequately to optimum doses of imatinib should be considered for entry into a clinical trial.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by phase II and III randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Across trials, response rates ranged from 41 to 65%, with an additional 32 to 36% of patients achieving stable disease.
- Phase III trials comparing 400 mg and 800 mg of imatinib daily detected no survival advantage with the higher dose but a significant increase in side effects. Data on progression-free survival are mixed, with one trial reporting a significant improvement with the higher dose and a second trial finding no significant difference.

POTENTIAL HARMS

- Phase III trials comparing 400 mg and 800 mg of imatinib daily detected a significant increase in side effects.
- Adverse effects include rash, edema, gastrointestinal bleeding, anemia, granulocytopenia, fatigue, nausea, and diarrhea.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- It is acknowledged that there are no randomized controlled trials (RCTs) comparing imatinib to no treatment or best supportive care thereby making it difficult to statistically quantify the benefits for progression free survival and overall survival conferred by imatinib. The Sarcoma Disease Site Group (DSG) has concluded that such trials will never be performed in the future in patients with unresectable or metastatic gastrointestinal stromal tumours (GISTs). In framing its recommendations, the Disease Site Group has also borne in mind the fact that treatment with imatinib in such patients has already gained wide acceptance among oncologists internationally.
- The recommendations for an initial dose of 400 mg daily is based on analyses of two randomized phase III trials that have compared two doses (400 mg versus 800 mg/day) of imatinib. A higher dose has not been shown to increase overall survival. There is a discrepancy in two-year progression-free survival, with one trial reporting a significant advantage in progression-free survival with the higher dose and one trial finding no significant difference.
- The treatment duration in responding patients, particularly those who achieve a clinical complete response is as yet undefined. For practical purposes, until further studies are done:
    - Patients with stable disease should be treated until disease progression. Phase III data beyond two years of continued therapy are not available.
    - Treatment should be discontinued if serious toxicity develops. The dose may be reduced or interrupted to allow side effects to resolve, then may be re-started.
    - For patients who achieve a complete clinical response and radiologic remission with imatinib, treatment should be continued indefinitely until further data is available regarding the optimum duration of therapy in such patients. This is based on the observation that the majority of patients relapse following cessation of therapy with imatinib.
- At present, there is insufficient evidence to support the use of imatinib as an adjuvant therapy in patients who have undergone initial complete resection of disease.
- Surgery may be considered for patients whose disease is rendered resectable following imatinib therapy or to remove residual disease in selected patients.
- At present, the use of neoadjuvant imatinib is not recommended.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, Sarcoma Disease Site Group. Imatinib mesylate (Gleevec) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 6. 23 p. (Evidence-based series; no. 11-7). [46 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr 6

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Sarcoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Sarcoma Disease Site Group disclosed information on potential conflict of interest. All members reported that they had no potential conflict of interest.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Imatinib mesylate (Gleevec™) for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Apr 6. Various p. (Practice guideline; no. 11-7). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 9, 2006. The information was verified by the guideline developer on June 26, 2006.

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